FORMULATION AND EVALUATION OF FLOATING TABLET ACECLOFENAC (NSAID)

A dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032.

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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Under the guidance of

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1. INTRODUCTION

FLOATING DRUG DELIVERY SYSTEM

The oral route is considered as the most promising safe and effective route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs.[1]

Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach.[2] This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).[3]

Currently, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro

dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems.[4]

FDDS is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. The retentive characteristics of the dosage form are not significant for the drugs that[5]

- are insoluble in intestinal fluids
- act locally
- exhibit site-specific absorption.

Criteria for HBS [6,7,8]

- ❖ Must have sufficient structure to form a cohesive gel barrier. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs
- ❖ Must maintain an overall specific gravity less than that of gastric content.
- ❖ Should dissolve slowly enough to serve as a reservoir for the delivery system.

Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include furosemide, cyclosporine, allopurinol ciprofloxacin and metformin. Drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlordiazepoxide and cinnarizine, the drugs prone for degradation in the intestinal pH (e.g.

captopril), and the drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamines, sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form.

Controlled release or Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs which are

- Administered two or more time a day
- Only absorbed in the upper GI regions
- Insoluble in water
- Targeted at sites in the upper GI tract
- Bioavailable through active transport mechanisms
- Irritating to the mucosa
- Unbalancing, irritating, or unsafe in the lower GI region
- More effective when plasma levels are more constant
- That are locally active in the stomach, that are locally active in the stomach
- That has an absorption window in the stomach or in the upper small intestine
- That are unstable in the intestinal or colonic environment
- Have low solubility at high pH values

PHYSIOLOGY OF STOMACH

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx). Oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of cecum, appendix, colon and rectum).[9] The wall of the GI tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spread and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes: interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a prominary function of cleaning up the residual content of the upper GI tract. The average length of the stomach is about 0.2 meters and the apparent absorbing surface area is about 0.1 m^2.

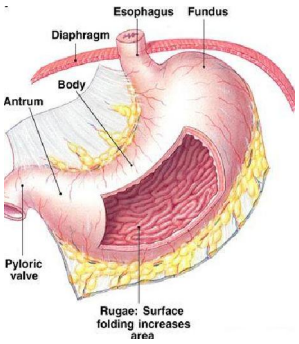


Figure 1 Anatomy of stomach.

Table 1 Anatomy and Physiology of GIT [10,11]

Section	*Average length (cm)*	*Villi present*	*Absorption mechanism*	*pH*	*Major constituents*	*TT of food (hr)*
Oral cavity	15-20	-	Passive diffusion, convective transport	5.2-6.8	Amylase, maltase, ptyalin, mucins	short
Esophagus	25	-	-	5-6	-	Very short
Stomach	20	-	Passivediffusion, convective transport	1.2-3.5	HCl, pepsin, rennin, lipase, intrinsic	0.25-3.00
Duodenum	25	+	Passive diffusion, convective transport, active transport, facilitated transport, ion pair pinocytosis	4.6-6.0	Bile, trypsin, chymotripsin, amylase, maltase, lipase, nuclease, CYP3A5	1-2
Jejunum	300	++	Passivediffusion, convectivetransport, active transport, facilitated transport	6.3-7.3	Amylase, maltase, lactase, sucrase, CYP3A5	-
Colon	150	-	Passive diffusion, convective transport	7.9-8.0	-	4-20
Rectum	15-19	-	Passive diffusion, convective transport, pinocytosis	7.5-8.0	-	Variable

GASTRIC pH

The gastric pH is not constant rather it is influenced by various factors such as diet, disease, presence of gases, fatty acids and other fermentation products, however the reported mean value of gastric pH in fasted healthy subjects is 1.1±0.5 and in fed state basal gastric secretion in women is slightly lower than that of men . The pH in the proximal duodenum may rise as high as 4 pH units from the stomach. This increase in pH caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralize acidic chime peristalses from the stomach. The mean pH value in fasted duodenum has been reported to be 5.8±0.3 in healthy subjects while the fasted small intestine has been observed to have a mean pH of 6.0±0.14. Passing from jejunum through the mid small intestine and ileum, pH rises from about 6.6 to 7.5.[12]

Gastric pH is an important consideration in selecting a drug substance, excipients and drug carrier(s) for designing intra gastric delivery systems.

GASTRIC MOTILITY AND TRANSIT TIME

The GI tract is always in a state of continuous motility. There are two modes of motility pattern the digestive mode and inter digestive mode. In case of fasted state an inter digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as inter digestive myo electric cycle or migrating myo electric complex (MMC), which is further divided into four phases.[13]

Table 2 Phases of myoelectric complex

Phase I	Period of no contraction.
Phase II	Period of intermittent contraction.
Phase III	Period of regular contractions at maximal frequency that migrate distally.
Phase IV	Period of transition between phase III and phase I.

FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.[14]

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Caloric content** – GRT can be increased by 4 to10 hours with a meal that is high in proteins and fats.
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.
- **Biological factors** – Diabetes and Crohn's disease, etc.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM[15,16]

Gastroretentive drug delivery systems have numerous advantages listed below

- ❖ The principle of HBS can be used for any particular medicament or class of medicament.
- ❖ The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious

with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

- The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
- The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
- Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.
- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
- Many drugs categorized as once-a-day delivery have been demonstrated to have sub optimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM[17,18]

- There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted.
- Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
- Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system .
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.
- Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.
- High variability in gastric emptying time due to variations in emptying process.
- Unpredictable bioavailability.

FLOATING DRUG DELIVERY SYSTEMS

The concept of FDDS was described in the literature as early as 1962. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.[19]

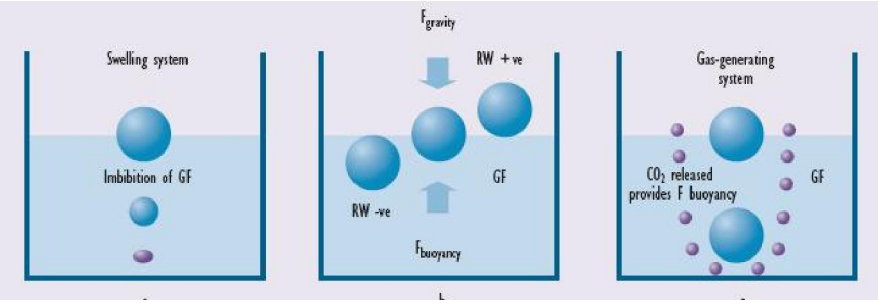


Fig 2 Mechanism of floating system

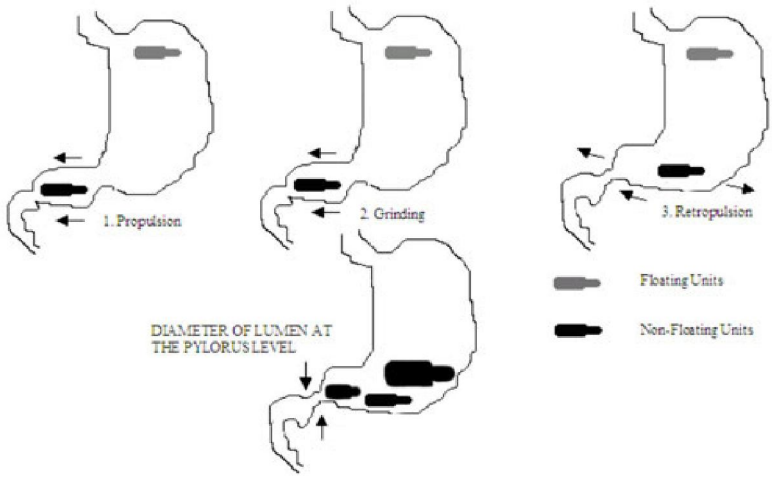


Fig 3. Intragastric residence positions of floating and nonfloating units.

Formulation of this device must comply with the following criteria

- It must have sufficient structure to form a cohesive get barrier.
- It must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010).
- It should dissolve slowly enough to serve as a drug reservoir.

Types of floating drug delivery systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1) Non- Effervescent FDDS

2) Effervescent FDDS

1) Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.[20,21]

Working Principle of Non- Effervescent-Type of FDDS

Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.

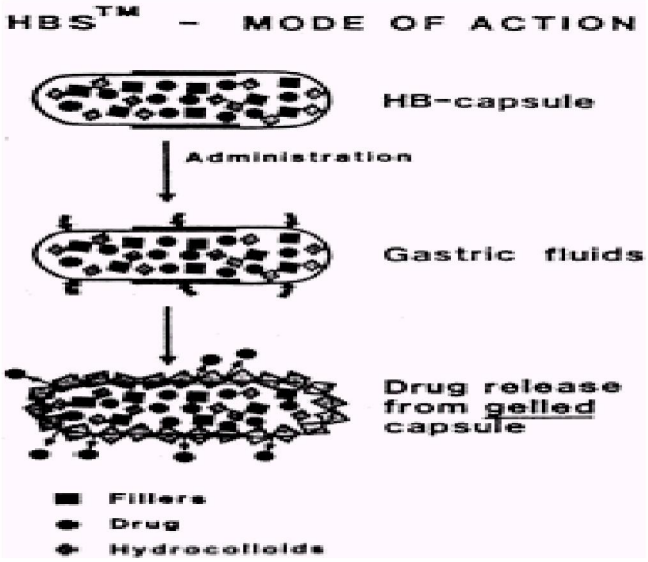


Fig 4 Working principle of non-effervescent type of FDDS.

The various types of this system are as:

A. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity.

They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

B. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.[22]

C. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.[23]

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.[24]

2) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

1. Gas generating systems
2. Volatile Liquid/Vacuum Containing Systems

1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for furosemide were developed by Ozdemir et al., 2000. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio (Singh and Brahma, 2000). One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The *in vitro* floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using hydroxypropylmethyl cellulose (HPMC) and polyethylene oxide (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and polyethylene oxide were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The *in vitro* results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high localized concentration of tetracycline and metronidazole.[25]

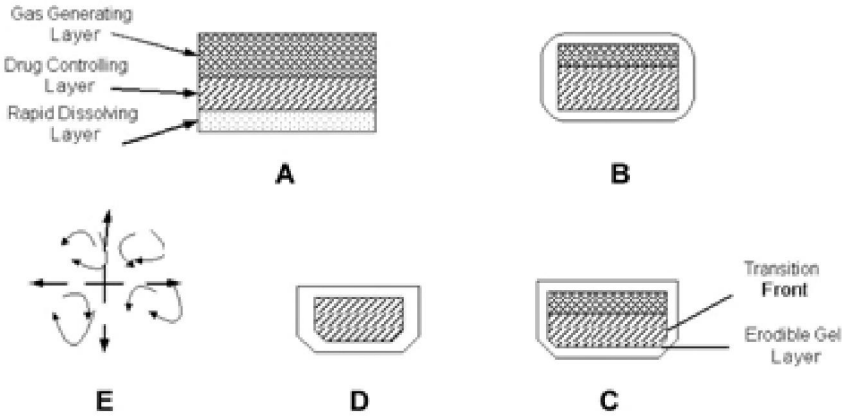


Fig 5 (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) And (E) Tablet erodes completely.

B. Floating capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during *in vitro* tests as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.[26]

C. Multiple unit type floating pills

The system consists of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.[27]

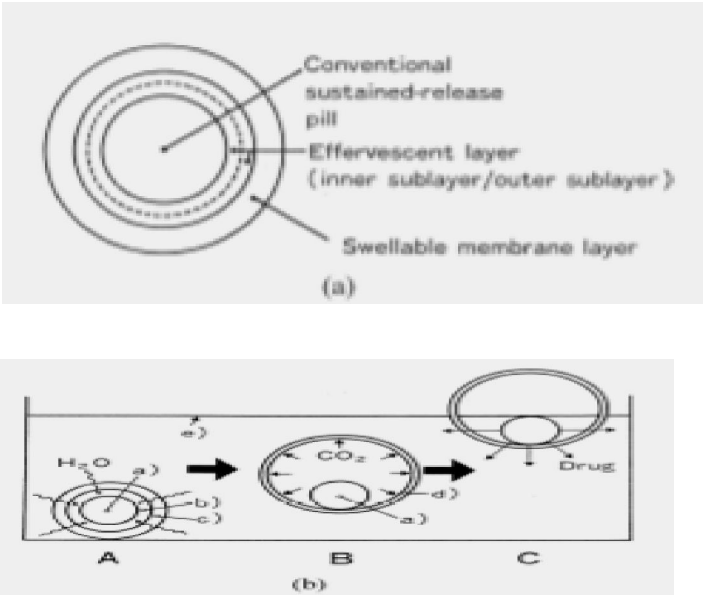


Fig 6 (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

D. Floating system with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The *in vivo* behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).[28]

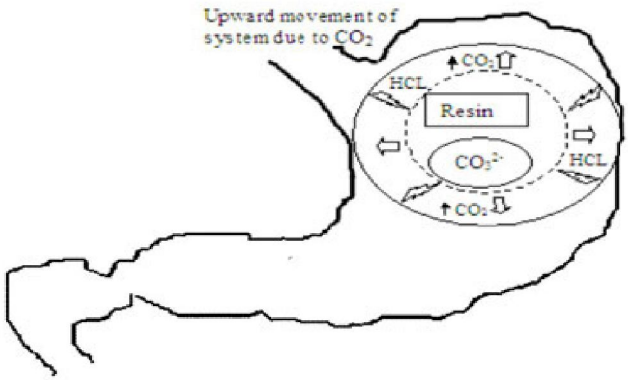


Fig 7 Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin.

2. Volatile Liquid / Vacuum Containing Systems

A. Intra-gastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

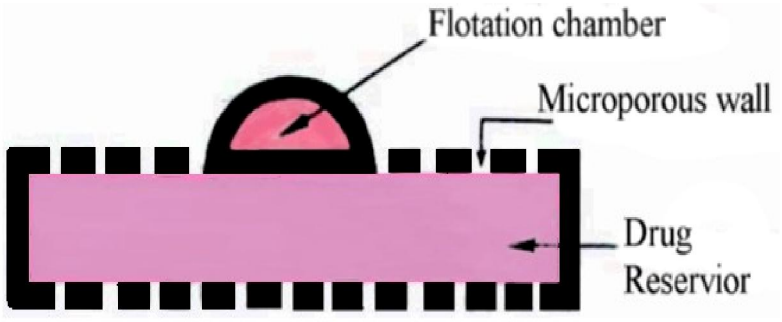


Fig 8 Intra gastric floating gastrointestinal drug delivery device.

B. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.[29]

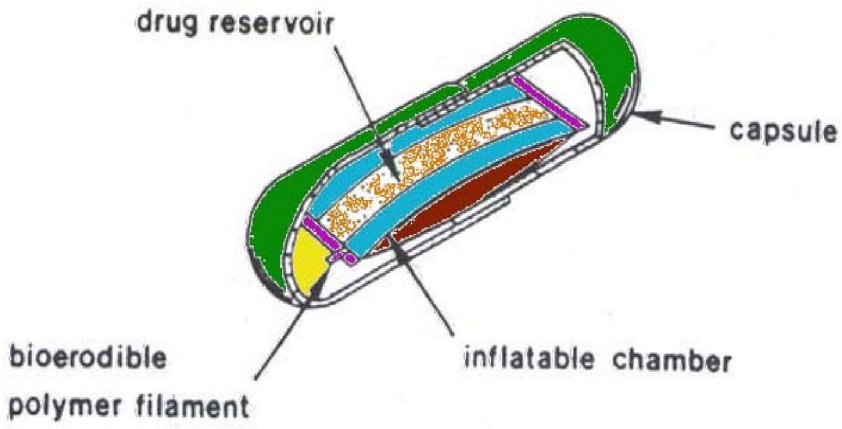


Fig 9 Inflatable gastrointestinal delivery system.

C. Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[30]

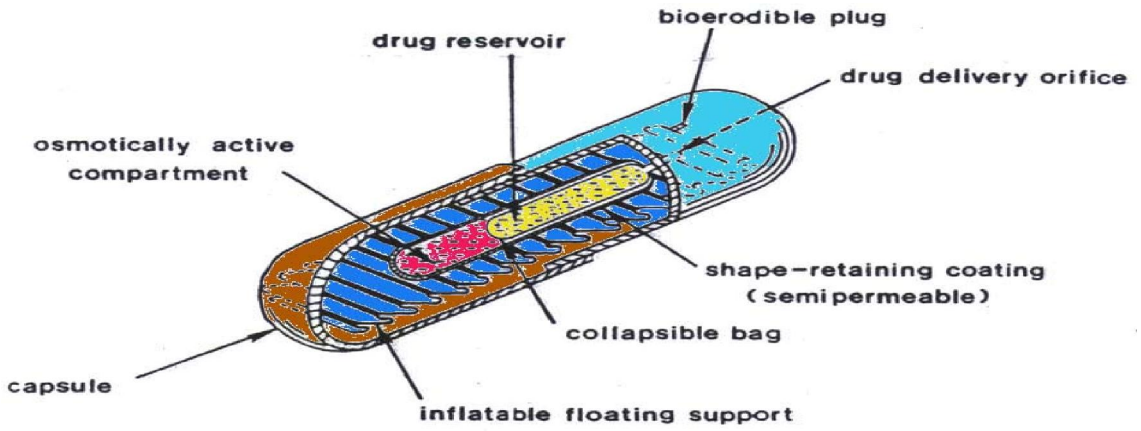


Fig 10 Intragastric osmotically controlled drug delivery system

Bioadhesive drug delivery system

Bioadhesion/Mucoadhesion for oral drug delivery

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a thorough understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment.

Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption.[31]

Various investigators have proposed different mucin-polymer interactions, such as

- Wetting and swelling of the polymer to permit intimate contact with the biological tissue
- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.
- Formation of weak chemical bonds
- Sufficient polymer mobility to allow spreading

- Water transport followed by mucosal dehydration .

As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time. [32]

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.[33]

Fig 11 Schematic illustration of the barrier formed by a raft-forming system

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have

therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core . Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used. [34]

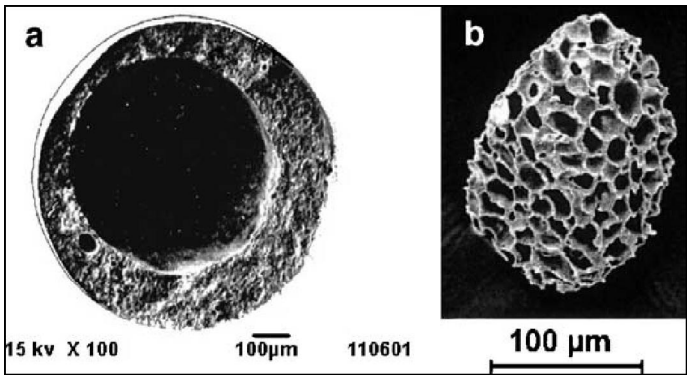


Fig 12 (a) Microballoons (b) Foam-particles.

Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release.

Unfoldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Caldwell et al., 1988 proposed different geometric forms (tetrahedron, ring or planar

membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule. [35]

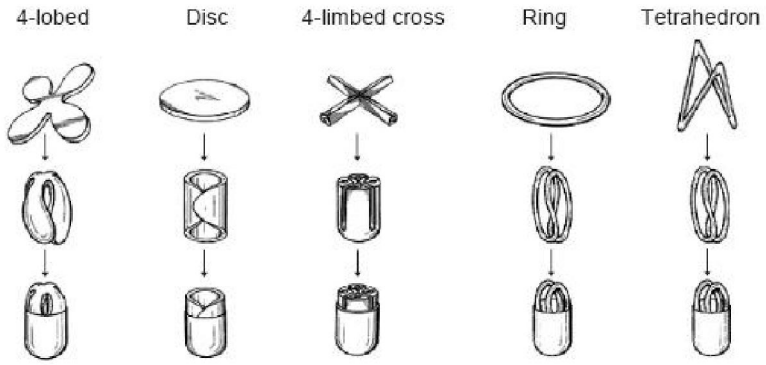


Fig 13 Different geometric forms of unfoldable systems

Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves.[36]

Mamajek and Moyer patented drug reservoirs, surrounded by a swellable expanding agent. Urquhart and Theeqwes (1984) developed a system containing tiny pills, with a very high swelling ratio enabling up to 50 fold volume increase. They were coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel. [37]

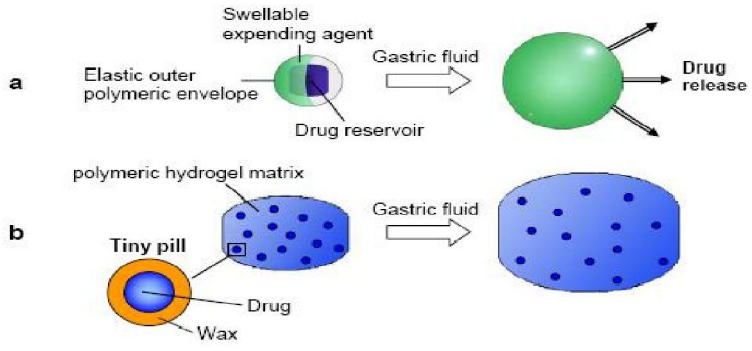


Fig 14Swellable systems developed by Mamajek and Moyer (a) Urquhart and Theeuwes (b).

Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification (Chen and park, 2000) with pore size ranging between 10 nm and 10 μm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size > 100 μm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) (Figure 17) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium).[38]

In vivo studies with dogs showed that under fasting conditions, the superporous hydrogel composite (i.e. containing Ac-Di-Sol) remained in the stomach for 2-3 hours. This time increased to >24 hours after feeding, even though the fed condition was maintained only for a few hours. After several hours (30 hours), fragmentation occurred and the composite was rapidly cleared.

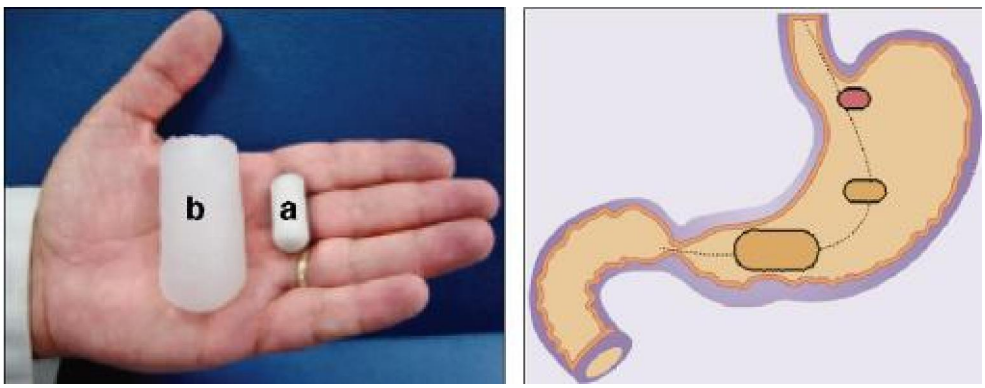


Fig 15 superporous hydrogel in its dry (a) and water-swollen (b) state.

schematic illustration of the transit of superporous hydrogel.

Magnetic system

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept. [39]

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.

- The use of hydrogels swelling in contact with the gastric juice.
- Osmotic systems, comprising an osmotic medium in a semipermeable membrane.
- Systems based on low-boiling liquids converting into a gas at the body temperature.

This imparts to the system a desired volume and provides for the drug release.

There are several problems for these systems, the main of which is the short swelling time (within several hours) insufficient for keeping the system in the stomach.

High density systems

Gastric contents have a density close to water (1.004 g /cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.[40]

Development and evaluation of GFDDS:

Formulation Development:

For the optimum design of a GFDDS, the key step is to understand the principles of G.I.dynamics such as gastric emptying. Small intestinal transit, colonic transit etc. Acquiring knowledge about the rate and extent of drug absorption from different sites of G.I sites, and factors that can alter or limit the absorption further aid I the designing the type of dosage form that is needed for a particular drug. For instance with drugs such as sulpiride, furosemide, theophylline and albuterol, which are predominantly absorbed from the upper part of the G.I tract, designing a gastric retention dosage form is a logical strategy for improving and extending their limited oral bioavailabilities[41-44]. For the formulation of a Hydrodynamically balances dosage forms, three major conditions must be met:

- It must have sufficient structure to form a cohesive gel barrier:
- It must maintain an overall density lower than that of gastric contents (reported as 1.004- 1.01g/cc) and
- It should dissolve slowly, enough to serve as a .reservoir. for the delivery system.

The task of designing a dosage forms to achieve a consistent and controlled residence in the stomach begins with selection of potential excepients that allow the formulation of the matrices having sustained delivery characteristics and a bulk density of less than unity. As far as the ideal floating dosage forms is concerned, it should have high buoyancy, adequate

mechanical strength, excellent acid resistance and a high drug releasing capacity in the stomach. Ideally water-soluble cellulose derivatives are best suited for such purposes.

In *vitro* and In *vivo* evaluation:

The various parameters that need to be evaluated for their effects on gastric retention time of buoyant formulations can mainly be categorized into following different classes. [45]

- Galenic parameters: dimeteral size (. cut-off size.), flexibility and density of matrices.
- Control parameters: floating time, dissolution, content uniformity, hardness and friability.
- Geometric parameters: shape.
- Physiological parameters: age, sex posture, food and bioadhesion. The test for buoyancy and in *vitro* drug release studies are usually carried out in simulated gastric fluid maintained at 37^{o}C. The in *vivo* gastric retentivity of a floating dosage forms is usually determined by gamma scintillography or roetgenography.[46] Studies are done, both under fasted and fed conditions using floating and non floating (control) dosage forms. It is also important that both dosage forms are non-disintegrating units, and human subjects are young and healthy.

INFLAMMATION

A morbid condition of any part of the body, consisting in congestion of the blood vessels, with obstruction of the blood current, and growth of morbid tissue. It is manifested outwardly by redness and swelling, attended with heat and pain. The classical signs of acute inflammation are pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function.

Inflammation (Latin, inflammare, to set on fire) is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.[47] Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen.

Without inflammation, wounds and infections would never heal. Similarly, progressive destruction of the tissue would compromise the survival of the organism. However, chronic inflammation can also lead to a host of diseases, such as hay fever, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). It is for that reason that inflammation is normally closely regulated by the body.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.[48]

Mechanism of action:

Most of the non-selective NSAIDs as inhibitors against cyclooxygenase enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isozymes. Cyclooxygenase catalyst to the formation of prostaglandins and thromboxane from arachidonic acid (itself is obtained from the porous phospholipid bilayer by the phospholipase A2). prostaglandin as a

(particular) messenger molecule in the inflammation process. This mechanism of action has been clarified after John received a Nobel Prize for the flap of his work (see aspirin ling mechanism of action). Recently discovered COX-3 could also have a role. [49]

2. AIM AND OBJECTIVES

Floating tablets are useful for those drugs that act locally in the gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine[45,46]

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is a newer non-steroidal anti-inflammatory drug (NSAID). Aceclofenac is a phenyl acetic acid derivative showing effective anti-inflammatory and analgesic properties mainly used in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac is rapidly and efficiently absorbed after oral administration but has a short half life of 3-4 h and requires multiple dosing for maintaining therapeutic effect throughout the day. Its biological half-life is very short, sustaining its anti-inflammatory activity only for a few hours and associated adverse effects; it is considered an ideal model drug for floating matrix drug delivery.

In fact there is a need to develop a dosage form to deliver aceclofenac in the stomach and to increase the efficiency of the drug, providing targeted action. The objective of this study was to prepare floating matrix tablets of aceclofenac using HPMC, carbopol and guar gum.

The purpose of this project was to prepare a floating drug delivery system of aceclofenac. Floating drug delivery system makes the dosage form to float on the gastric fluid. These can remain in the gastric part for several hours and hence significantly prolong the gastric residence time of the aceclofenac.

The overall aim and object of the present work was

- Formulation of floating tablets for Aceclofenac (AF1 – AF5)
- Evaluation of formulated product (AF1 – AF5)

3. LITERATURE REVIEW

- **Akbari *et al*, (2010)**[50] prepared floating tablets using direct compression techniques using polymers like HPMC K4M and HPMCK100M. The HPMC polymer alone is unable to control release rate. It releases drug >90% in four to six hours. In combination with Xanthan gum it release >90% in eight hours. The results indicate that gas generated gastroretentive floating tablets of famotidine containing HPMCK100M and Xanthan gum provide better options for controlled release action and improved bioavailability.
- **Ravi Kumar *et al,* (2009)** [51] developed floating matrix tablets of aceclofenac to prolong gastric residence time and to increase bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Floating matrix tablets containing 100 mg aceclofenac were developed using different bees wax combinations. The tablets were prepared by melt granulation technique, using polymers such as hydroxypropylmethylcellulose (HPMC K15M), ethyl cellulose, bees wax, cetyl alcohol, glycerin monostearate alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent.
- **Orazio SL *et al,* (2008)**[52] studied in vivo by resultant-weight measurement and in vivo by ϒ-scintigraphy experiment in humans, the floating behavior of system obtained by modules assembled in void configuration. the floating of the system immediately and lasted for more than 5 h.
- **Quan Liu and Reza Fassihi (2008)**[53] prepared a zero order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro-retentive system which were prepared as two multilayer delivery systems. First formulation compressed a

triple layer based on PEO while the second formulation was a bilayer composite matrix system composed of HPC and HPMC. The observation showed that the systems demonstrated controlled release kinetics independent of pH changes with about 99% of dose being released around 18h. The maintenance of constant surface area during dissolution is critical for zero-order drug delivery. The burst release suppression effect brought about by raped initial swelling and controlled erosion of layers provided for programmed controlled delivery and enhanced floatation

- **Jaimini *et al,* (2007)**[54] investigated the effect of citric acid on drug release profile. The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. Decrease in the citric acid level increased the floating lag time but tablets floated for longer duration. A combination of sodium bicarbonate (130mg) and citric acid (10mg) was found to achieve optimum *in vitro* buoyancy.
- **Manoj *et al*, (2007)**[55] prepared floating drug delivery system of diltiazem hydrochloride using polymers such as HPMC K100M CR and compritol 888 ATO, alone and in combination. The effect of sodium bicarbonate and succinic acid on drug release was investigated. The high level of both methocel K100M CR and compritol 888 ATO favoured the preparation of floating controlled release of diltiazem tablets. It was observed that incorporation of succinic acid in the formulation nullified the effect of the acidic dissolution media on the drug release in this formulation, methocel K100M CR retards the release by diffusion mechanism and compritol 888 ATO decreases the hydration of matrix and retards the release by erosion mechanism owing to its hydrophobic property. Together, these polymers retard the release of drug using different mechanisms

- **Talukder *et al,* (2006)**[56] developed a floating multi particular system with potential for intra-gastric sustained drug delivery .Cross-linked beads were made by using low methoxylated pectin and sodium alginate .Riboflavin, tetracycline and methotrexate were used as model drugs for encapsulation. It appeared that the nature of cross-linking, drug solubility and production approach were important and provide the opportunity and potential for development of a gastro retentive drug delivery system.
- **Narendra *et al,* (2006)**[57] developed an optimized gastric floating dosage form containing metoprolol tartrate as model drug. The results showed that total polymer content to drug ratio and polymer to polymer ratio significantly affect the floating time and drug release property of formulated bilayer tablets.
- **Patel *et al*, (2006)**[58] investigated an intragastric drug delivery system for cefuroxime axetil to evaluate the contribution of HPMC K4M/HPMC K100 LV ratio and the SLS on drug release. Formulations were evaluated for *in vitro* buoyancy and drug release study using USP 24 paddle type dissolution apparatus using 0.1 N HCl as a dissolution medium. It was found that the polymer blend and SLS greatly affect the dissolution parameters.
- **Bardonn *et al*, (2006)**[59] reviewed and summarized the important physiologic parameters, which act upon the gastric residence time and different drug delivery systems i.e. high-density, intragastric floating, expandable, superporous hydrogel, mucoadhesive and magnetic systems
- **Shweta *et al*, (2005)**[60] reviewed on floating drug delivery systems with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This

review also summarizes the *in vitro* techniques, *in vivo* studies to evaluate the performance and application of floating systems, and applications of these systems.

- **Basak SC *et al,* (2004)**[61] formulated a floating matrix using ciprofloxacin as model drug.the formulation consist of sodium bicarbonate (gas generating agent), HPMC , lactose and PVP .the in vivo drug release studies showed sustained release of ciprofloxacin up to 80-89% for 8h.
- **Ozdermis *et al,* (2004)**[62] prepared floating dosage to enhance the bioavailability of furosemide. The solubility was increased by forming inclusion complex with betadex (beta cyclodexterin). Dissolution studies and floating time was studied. The plasma AUC values of floating dosage forms were about 1.8 times greater than those of the conventional tablet.
- **Eikheshen *et al,* (2004)**[63] prepared a sustained release floating system for verapamil HCl using different polymers, which are HPMC, HPC and ethyl cellulose.Floating was maintained gy adding effervescent mixture of sodium bicorbonates and citric acid.Results showed that HPMc has floating property.
- **Wei *et al*, (2004)**[64] developed a pH dependent floating sustained release tablet for gastric retention of 5-FU and prepared two layer floating tablet wherein floating ability is independent of the gastric acidity variation.
- **Li *et al*, (2003)**[65] investigated the effect of formulation variables on the calcium release and floating properties of the delivery system by using 2x3 factorial designs by using different grades of Hydroxypropylmethylcellulose (K100LV and K4M) and carbopol. They reported that by increasing the HPMC viscosity the release rate decreases and floating properties improved as the viscosity of the polymer is increased. Carbopol (CP934) incorporation was found to compromise the floating capacity of floating and release of calcium

- **Shoufeng Li *et al,* (2002)**[66] found that both HPMC viscosity, the presence of carbopol and their interaction had significant impact on the release and floating properties of the delivery system. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K100LV) was shown to be beneficial than higher viscosity polymer (K4M) in improving the floating properties of GFDDS. Incorporation of Carbopol, however, was found to compromise the floating capacity of GFDDS and release rate of calcium.
- **Nur and Zhanj (2000)**[67] prepared captopril floating and bioadhesive tablets using two grade of HPMC (400 and 15000cps) and carbopol 934P. *In vivo* dissolution was carried out in simulated gastric fluid (enzyme free) at 37 ± 0.1°C using the USP type II method. Compared to conventional tablets, release of captopril from these floating tablets was apparently prolonged (24hrs). Tablet hardness was found to be a determining factor with regard to the buoyancy of the tablets.
- **Iannuccelli *et al*, (2000)**[68] used PVP solid dispersions for the controlled release of furosemide from a floating multiple-unit system. The complete dose release over the actual intra-gastric residence time of the system (about 8 hr) was achieved by loading both the core and the membrane forming the units with 1:5 furosemide: PVP solid dispersion. Physicochemical analysis suggested that amorphous state of furosemide enhanced drug solubility and dissolution rate, which led to the desired release profile from the floating units.
- **Ozdemir *et al*, (2000)**[69] developed floating bilayer tablet of furosemide- cyclodextrin inclusion complex. They determined the gastric residence time using radiographs by adding $BaSO_4$ and reported that the tablet stayed in stomach for 6 hours. Also the bioavailability of furosemide from floating tablet was about 1.8 times that of the conventional tablet and also significant *in vitro – in vivo* correlation was detected.

- **Krogel and Bodmeier (1999)**[70] developed and evaluated floating drug delivery system based on effervescent core and a polymeric coating. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit RS, RL and NE) and cellulose (cellulose acetate, ethyl cellulose) polymer, which primarily determined the type of delivery system, a polymer coating with a high elongation value and high water low carbon dioxide permeability was selected (Eudragit RL/ acetyl tributyl citrate 20%w/w) in order to initiate the effervescent reaction and the floating process rapidly. HPMC was also added in the core to retard drug release. The composition and hardness of the tablet core and the composition and hardness of the coating could control the time of flotation.
- **Lee *et al,* (1999)**[71] prepared floating acrylic resin microspheres with an internal hollow structure by a solvent diffusion and evaporation method. The yield of microspheres depended on the diffusion rate of ethanol and/or isopropanol in the gastric phase. Best results were obtained at the volume ratio of Ethanol: Isopropanol: dichloromethane (8:2:5). When a drug had low solubility in dichloromethane, the loading efficiency was the lowest.
- **Chen and Hao (1998)**[72] studied the *in vitro* performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent materials are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent material on the dissolution kinetics were studied. They concluded that the release of Verapamil from the capsule followed Higuchi release model. However, when effervescent material was added, the system showed a zero-order release.
- **Atyabi F *et al,* (1996)**[73] prepared floating ion exchange resin beads. Beads were loaded with bicarbonate and coated with a semi permeable membrane .These beads

exhibited a prolonged gastric residence due to release of carbon dioxide that was trapped inside the coating of the beads .A model drug theophylline has been loaded on to the resin .The beads produced a controlled release pattern of drug.

- **Menon *et al,* (1994)**[74] reported the formulation of a monolithic floating dosage form for Furosemide using factorial design keeping the drug to polymer ratio, polymer to polymer ratio and polymer grade as the three factors. The optimized formulation thus obtained was found to have a good *in vitro - in vivo* correlation.
- **Desai and Bolton (1993)**[75] developed controlled release floating tablets of the theophylline using agar and light mineral oil. Tablets were made by dispersing drug and mineral oil mixture in a warm agar solution. The resultant mixture was poured into tablets moulds, which on cooling and air-drying formed floatable CR tablets. The light mineral oil was essential for the floating property of the tablets since relatively high amount of the drug (75%) was used.
- **Gerogiannis *et al*, (1993)**[76] examined the floating and swelling characteristics of several excipients used in controlled release technology. The floating behavior was evaluated with resultant weight measurements, while a gravimetric method was employed for studying their swelling. The results indicated that higher molecular weight polymers had slower rates of polymer hydration and usually followed by enhanced floating behavior.

DRUG PROFILE- ACECLOFENAC [77,78]

Generic Name

Aceclofenac

Trade Name

Acefen, Acefen p, Acenac, Dolokind

Molecular mass

354.18472g/mol

Molecular formula

$C_{16}H_{13}CL_2NO_4$

Melting point

149-153^{O}C

IUPAC name

2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl] ox acetic acid

Aceclofenac is an orally administered phenyl acetic acid derivatives with effects on a variety of inflammatory mediators.

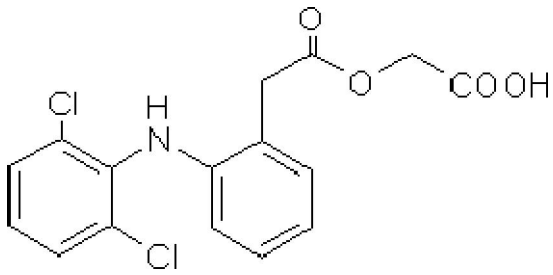


Fig 16 Aceclofenac

Aceclofenac contains not less than 99.0% and not more than the equivalent of 101.0 percent of 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid.

It is a white or almost white crystalline powder. It is an effective analgesic and anti-inflammatory agent with a good tolerability profile. Through its analgesic and anti-

inflammatory properties, aceclofenac provides symptomatic relief in a variety of painful conditions.

Solubility

Practically insoluble in water, freely soluble in acetone, soluble in alcohol.

Storage

In an air tight container, protected from light.

Pharmacology

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins.

The drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E_2 (PGE2) production. Effects on cell adhesion molecular from neurophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood assays, with selectivity for Cox-2 being evident.

Aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1 activity. In vitro data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritis cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyacelofenac has chondroprotective properties attributable to suppression of IL-1 mediated promatrix metalloproteinase production and proteoglycan release.

In patients with osteoarthritis of the knee, aceclofenac decrease pain reduces disease severity and improves the functional capacity of the knee. It reduces joint inflammation, pain

intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis.

PHARMACOKINETICS

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (7.99%). The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion.

Aceclofenac is metabolized to a major metabolite, 4'-hydroxyaceclofenac and to a number of other metabolites including 5-hydroxyaceclofenac, 4'-hydroxydiclofenac, diclofenac and 5-hydroxydiclofenac. Renal excretion is the main route of elimination of aceclofenac with 70 to 80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half-life of the drug is approximately 4 hours.

Adverse Drug Reaction

Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrhea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%), pancreatitis (0.1%).

Although the incidence of gastro intestinal adverse events with aceclofenac was similar to those of comparator NSAIDS in individual clinical trials, withdrawal rates due to these events were significantly lower aceclofenac than with ketoprofen and tenoxicam.

Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), and rare cases: par aesthesia and tremor.

Dosage and Administration

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening. There is no evidence that the dosage of aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDS caution should be exercised.

POLYMER PROFILE

HPMC[79,80,81]

Structural unit

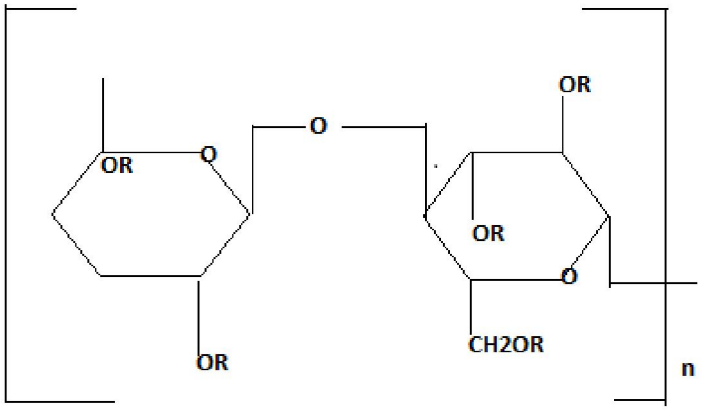


Fig 17 Structure of HPMC

Non-proprietary Name

Hydroxymethylcellulose.

Synonyms

Hydroxypropylmethyl ether, methylhydroxypropylcellulose methylcellulose, methocel.

Chemical name

Cellulose, 2-hydroxypropyl methylcellulose.

Application

Hypromellose is widely used in oral and topical pharmaceutical formulations. Hypromellose is used as tablet binder, in film coating and as an extended release tablet matrix. Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes.

Hypromellose is also used as a suspending agent and thickening agent in topical formulations particularly in ophthalmic preparations. Hypromellose is also used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses.

Solubility

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol and ether. But it is soluble in mixtures of methanol and dichloromethane and mixtures of water and alcohol.

Description

Hypromellose is an odorless and tasteless, white or creamy or granular, powder.

pH

1% w/w solution 5-8

Viscosity

A wide range of viscosity HPMC is available. HPMC E50 Viscosity 50 mPas.

Stability storage

Hypromellose is stable powder, but after drying it is hygroscopic. Solutions are stable at ph 3-11 increasing temperature reduced the viscosity of solutions. Hypromellose is aqueous solutions are comparatively enzyme-résistance, providing good viscosity stability during long-term storage. It is liable to microbial spoilage; benzalkonium chloride is commonly used preservative.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents.

CARBOPOL 940[79,80,81]

Nonproprietary Names :

BP: Carbomers,

PhEur: Carbomera

USPNF: Carbomer

Synonyms

Acritamer; acrylic acid polymer; Carbopol; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

Chemical Name

Carbomer

Molecular Weight :

$3x10^6D$

Functional Category

Bio adhesive, Emulsifying agent, suspending agent, tablet binder, viscosity increasing agent, Release modifying agent.

Application in Pharmaceutical Formulation or Technology

Carbopol 940 is used mainly in liquid or semisolid pharmaceutical formulations as suspending or viscosity increasing agent. Formulation including Creams, gels and ointments for in ophthalmic rectal and topical preparations. In the tablet formulations carbomers are used as dry or wet binder and as a rate controlling excipients.

Carbomer resins have also been investigated in the preparation of sustained release matrix beads, as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive patch for cervical patch and for intranasally administered microspears, in magnetic granules for site specific drug delivery to the esophagus and in oral mucoadhesive controlled drug delivery system

Stability and Storage Conditions

Carbopol is stable and should be stored in tight containers.

Incompatibilities

Carbomer are discolored by resorcinol and are incompatible with phenol, cationic polymers strong acids and high level of electrolyte

Safety

It is regarded as essentially nontoxic and nonirritant materials.

GUAR GUM[79,80,81]

Synonyms

Galactosol; Gaurflour; jaguar gum; Meprogat.

Chemical name

Galactomannan polysaccharide

Empirical formula

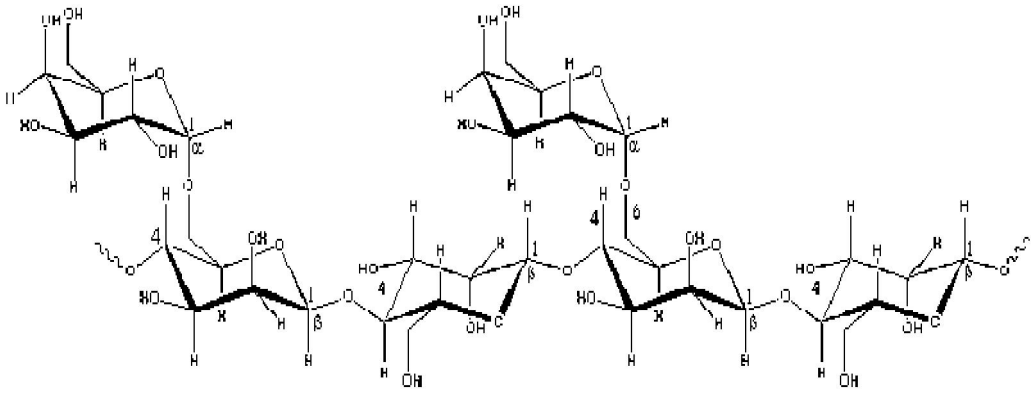
$(C_6H_{12}O_6)_n$

Molecular weight

≈ 220 000

Structural formula

Gaur gum consists of linear chains of (1→4)-β-D-manno-pyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is 1: 1.4 to 1:2.



Description

The USPNF 20 describes guar gum as a gum obtained from the ground endosperms of cyamopsis tetragonolobus (Fam: Leguminosae).

Colour

White to yellowish white

Odour

Odorless or nearly odorless

Taste

Bland taste

Texture

Powder

Acidity / Alkalinity

pH 5.0 to 7.0 (1% w/v aqueous dispersion)

Viscosity

4.86 Pas for 1% w/v dispersion

Solubility

In organic solvents disperses and swells immediately in cold or hot water to form a highly viscous and thixotropic solution.

Functional category

Suspending agent, Tablet binder, Tablet disintegrate, Viscosity increasing agent

Applications in pharmaceutical technology

- Used in solid dosage forms as a binder (up to 10%) and disintegrant
- Used in oral and topical products as a suspending, thickening (up to 2.5%) and stabilizing agent (1%)
- Used in colon targeted drug delivery systems
- Used as an appetite suppressant
- Also, used in cosmetic and food products

Storage

It should be stored in a well closed container and kept in cool and dry place.

Incompatibilities

It is incompatible with acetone, alcohol, tannins, strong acids and alkalis.

Presence of borate ions in distilled water, will prevent

SODIUM CARBOXYMETHYLCELLULOSE [79,80,81]

Brand name

Akucell; Aquasorb; Blanose; Cellulose gum; Cmc Sodium; E466; Finnfix; Nymcel; SCMC; Sodium Carboxymethylcellulose; Sodium Cellulose Glycolate; Sodium Cmc; Tylose Cb.

Description

Color

white to almost white,

Odor

Odorless

Solubility

Practically insoluble in acetone, ethanol, ether, and toluene.

Functional category

Coating agent; tablet and capsule disintegrant; tablet binder; stabilizing agent; suspending agent; viscosity-increasing agent; water-absorbing agent.

Applications in pharmaceutical formulation

- Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.
- Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions.
- Carboxymethylcellulose sodium is also used in cosmetics, toiletries and incontinence, personal hygiene, and food products.

Stability

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high-humidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water.

Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9.

Storage

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.

The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. Precipitation may occur at pH <2, and also when it is mixed with ethanol (95%).

Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

SafetyCarboxymethylcellulose sodium is used in oral, topical, and some parenteral formulations. The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.

4. PLAN OF WORK

1. PREFORMULATION STUDIES

i. Compatibility studies

ii. Flow property

- Bulk density
- Tapped density
- Hausner's ratio
- Carr's index
- Compressibility index
- Angle of repose

2. FORMULATION STUDIES

Formulation of floating tablets of aceclofenac using different polymers (AF1-AF5)

3. EVALUATION STUDIES

a. Hardness, Friability, LOD, average weight

b. Buoyancy lag time.

c. Duration of floating

d. Drug content

e. Swelling study

f. Dissolution

5. MATERIALS AND METHODS

Table 3 Materials Required

S.NO	MATERIALS	SOURCE
1	Aceclofenac	Medopharm, Chennai
2	HPMC	Otto Chemika-Biochemika reagents, Mumbai
3	Carbopol 940	Otto Chemika-Biochemika reagents, Mumbai
4	Guar gum	Loba Chemie Pvt, Ltd,Mumbai
5	Acacia gum	Loba Chemie Pvt, Ltd,Mumbai
6	Citric acid	Sisco Research Laboratories Pvt Ltd, Mumbai
7	Sodium bicarbonate	Sisco Research Laboratories Pvt Ltd, Mumbai
8	SCMC	Indian Research Products, Chennai
9.	Magnesium stearate	Loba Chemie Pvt, Ltd, Mumbai

Table 4 Equipments required

S.NO.	EQUIPMENT	SOURCE
1	Tablet compression machine	Rimek, minipress, UK
2	Hot air oven for drying	Hicon, New Delhi.
3	Electronic balance	Sartorious, Germany
4	Bulk density apparatus	Veego, Mumbai
5	Dissolution apparatus	Electrolab Mumbai
6	Friabilator	EF - 2 Electrolab, Mumbai
7	Hardness testing apparatus	Tablet hardness tester, Monsanto
8	Melting point apparatus	Campbell Electronics, Mumbai
9	pH meter	Digisun Electronics. Hyderabad
10	FTIR	Alphar T0, Bruker, New Delhi
11	UV-Spectrophotometer	UV-1700, Shimadzu, Mumbai

METHODS

PREFORMULATION STUDIES [80,81]

Preformulation is defined as application of biopharmaceutical principles to the physicochemical properties of the drug. It is a phase of R & D process.

FTIR Spectroscopy

IR spectra of aceclofenac, was obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets.

Melting point

Aceclofenac MP was measured by capillary tube method.

Loss on drying

10gms Aceclofenac was heated to a temperature of 105ºC in hot air oven until it remains constant weight. The formula was

$$\text{Percentage LOD} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \text{ X } 100$$

The results were recorded and given in the results and discussion.

Angle of repose

It was measured by fixed funnel technique. In this technique a funnel containing aceclofenac was kept at a fixed height, and it was allowed to flow to the surface which contains graph paper. This is due to gravitational force. The height and radius of the heap formed was measured. The formula for angle of repose (θ) was

$$\theta = \tan^{-1}(h/r)$$

The results were recorded and given in results and discussion.

Bulk density & Tapped density:

Bulk densities of granules were determined by pouring gently 20 gm of sample through a glass funnel into a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density and tapped density were calculated by the formula

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Volume of Powder (Untapped)}}$$

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Volume of Powder (Tapped)}}$$

The results were recorded and given in the results and discussion.

Compressibility Index

CI of the powder was determined from the bulk and tap density as follows[4]

$$\text{Percentage Compressibility Index} = 100 \text{ X } \frac{(\text{Tapped Density - Bulk Density})}{\text{Tapped Density}}$$

The results were recorded and given in the results and discussion.

Hausner's ratio

It was calculated as

$$\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

The results were recorded and given in the results and discussion.

COMPATIBILITY STUDIES

IR Spectroscopy

IR spectra of pure aceclofenac, polymer and combination of aceclofenac with polymers were obtained by using Perkin-Elmer Fourier transform infrared spectrophotometer. The scanning range used was 4000 to 400cm^{-1}. [82]

The results were recorded and given in the results and discussion.

STANDARD GRAPH OF ACECLOFENAC:

Standard graphs of the drug were prepared using standard aceclofenac solution in acid buffer pH 1.2, phosphate buffer pH 6.8 & pH 7.4 containing 5 to 50µg. The absorbance was measured at 275nm. Linear relationship was observed with absorption to concentration of drug. The values of absorbance related to concentration were given in table 6 and graphs were given in fig 19.

FORMULATION

Table 5 Formulation trails of Aceclofenac floating tablets (AF1 – AF5)

S.NO	INGREDIENTS	AF1 (mg)	AF2 (mg)	AF3 (mg)	AF4 (mg)	AF5 (mg)
1	Aceclofenac	200	200	200	200	200
2	HPMC	200	_	_	100	100
3	Carbopol 940	_	200	_	100	_
4	Guar gum	_	_	200	_	100
5	Citric acid	20	20	20	20	20
6	Sodium CMC	20	20	20	20	20
7	Sodium bicarbonate	20	20	20	20	20
8	Magnesium stearate	5	5	5	5	5
9	Talc	5	5	5	5	5
	Total Weight	470	470	470	470	470

Aceclofenac floating tablets were prepared by direct compression method using excipients and polymers to release the drug sustainably after administration

Accurately weighed quantities of excipients were placed in a mortar and gradually mixed with constant kneading to ensure homogenous mass. Then the homogenous powder was passed through sieve number 40 and the powder was retained on sieve number 100. Then the powder was lubricated with magnesium stearate and talc. Then the powder was directly compressed into tablets on a tablet punching machine.

EVALUATION OF FLOATING TABLETS

Standard graph of Aceclofenac

The λ max of aceclofenac in 0.1 N HCl was scanned to be 275 nm using UV spectrometer. The standard graph of aceclofenac was dissolved in required quantity of 0.1N HCl and made up the volume 100 ml using 0.1N HCl. To obtain the stock solution of concentration 1mg/ml, from this 1 ml was taken and diluted to 100ml using 0.1N HCl to obtain working stock solution of concentration. From the above solutions 5, 10, 15, 20,2 5ml was taken to dilute to 10ml using 0.1N HCl to obtain the concentration of 5,10,15,20,25µg/ml.

EVALUATION OF PHYSICAL PROPERTIES

i. Weight variation

Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average by more than the percentage shown in table below and none deviates by more than twice that percentage.

ii. Friability

20 tablets were weighed and placed in the Roche friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus, after 100 revolutions, the weighed again. The friability was determined as the percentage loss in the weight of the tablets. A loss of less than 0.5 to 1% in weight is generally considered acceptable.

iii. Hardness

Hardness was measured using Pfizer hardness tester which measure the pressure required to break the diametrical placed tablets by the pressure with coiled spring.

iv. Content uniformity :

It is the amount present in each formulation for formulation (or tablets)

Tablets from formulation was taken and dropped in 100ml 0.1N HCl in a beaker. After 24 hrs or when the drug is released completely the same sample was withdrawn (about 1ml) and diluted to 10ml with 0.1N HCL and absorbance was taken at 275nm using UV spectrometer. From the standard graph % drug release was calculated.

v. Thickness:

The thickness of the tablet is measured by using screw gauge. It gives the changes in weight variation of the tablet

vi. Floating lag time:

The floating lag time is determined in order to assess the time taken by the dosage to float on the top of the dissolution medium, after placing the dosage form in the medium.

vii. Floating time:

It is the time the tablet constantly floats on the dissolution medium (i.e duration of floating) in the dissolution medium.

viii. Dissolution studies:

Aceclofenac floating tablets were kept in dissolution medium 0.1N HCl (900ml) for initial 2 hours and operated at temperature $37\pm0.5^{0}C$ and rotated at 75 rpm. Then pH 6.8 phosphate buffer (900ml) was used as dissolution medium. Freshly prepared dissolution medium is used always. Type paddle apparatus is used. About 5ml of the dissolution medium was pipetted out for every 15, 30, 60, 120, 240, 480, 960 mins and the volume was adjusted using by replacing with 5ml of 0.1N HCl or with pH 6.8 phosphate buffer. The samples collected were analysed using UV spectrometer at 275nm.

6. RESULTS AND DISCUSSION

Preformulation studies:

In preformulation studies drug characteristics was performed and results were complies with pharmacopoieal values

A. **Standard graph of Aceclofenac:** the dissolution studies for the floating tablet have to be conducted in 0.1N HCl. Hence, UV spectrum of aceclofenac in 0.1N HCl was recorded on Elico spectrophotometer. The spectrum has shown λmax of 275nm which is selected for the construction of standard graph of aceclofenac in 0.1N HCl.

   A plot of absorbance Vs concentration of aceclofenac in 0.1N HCl is found to be linear in the concentration range of 5-25µg/ml indicating a perfect relation between drug concentration and absorbance

Table-6 Standard plot of Aceclofenac

CONCENTRATION (µg/ml)	ABSORBANCE
5	0.065
10	0.131
15	0.192
20	0.252
25	0.321

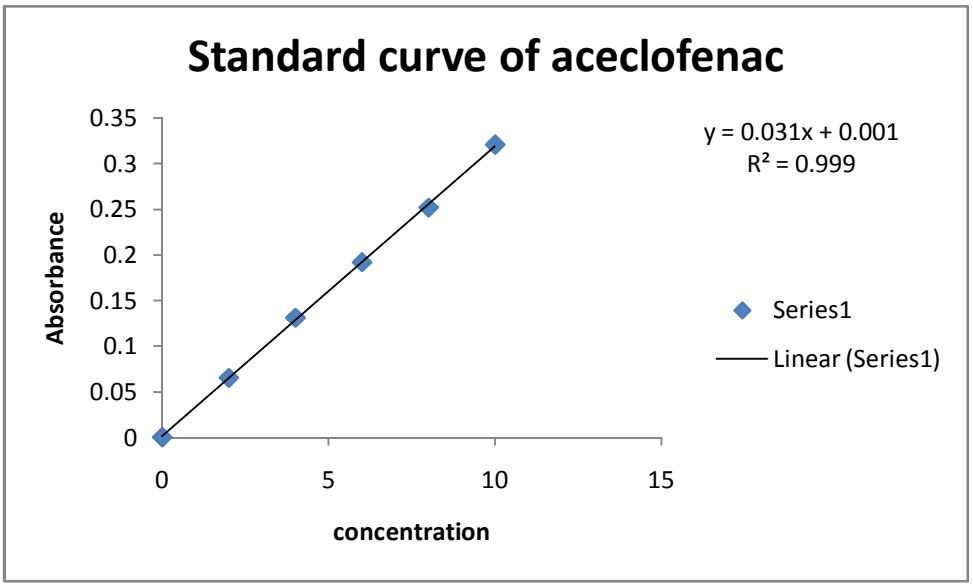


Fig-19 Standard curve of aceclofenac

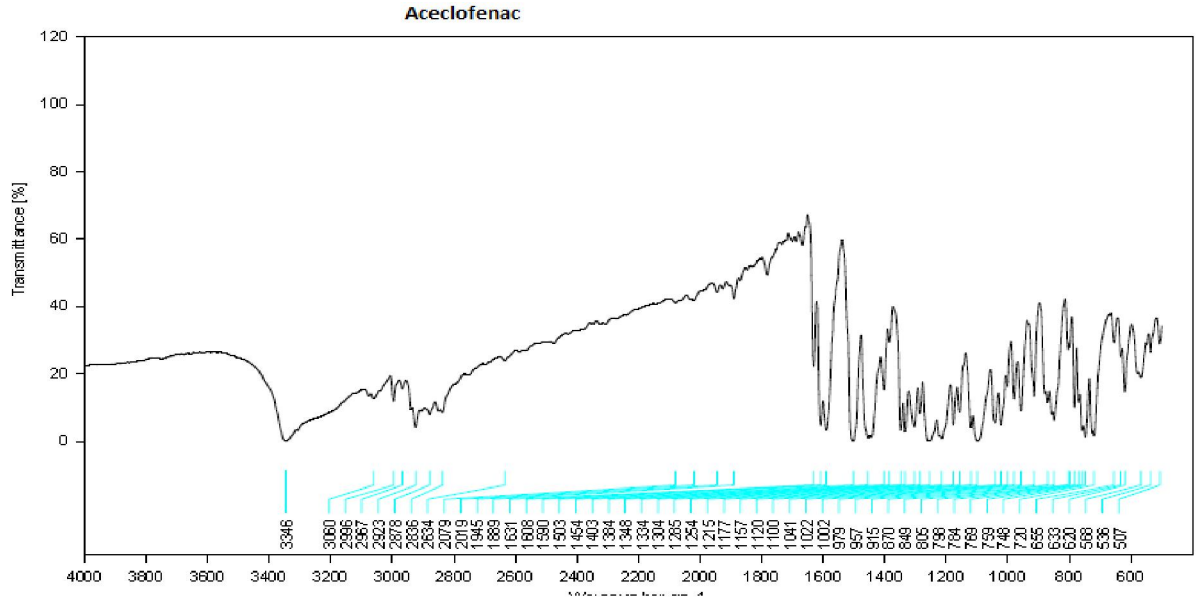


Fig 20 FTIR of Aceclofenac

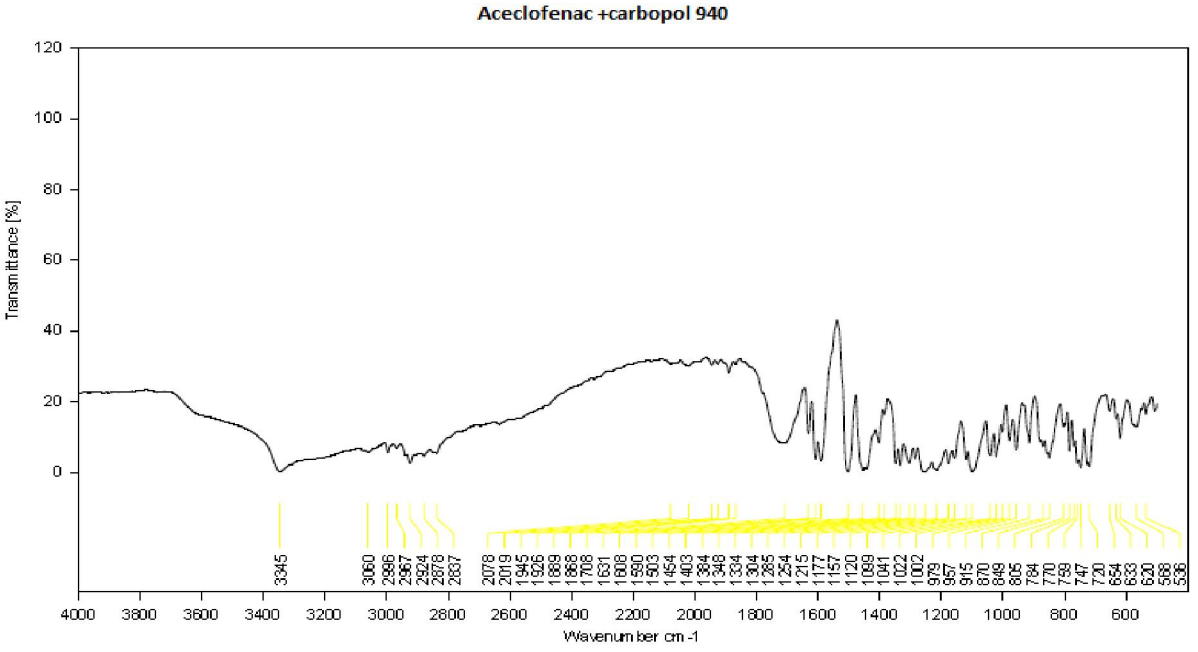


Fig 21 FTIR of Aceclofenac + Carbopol 940

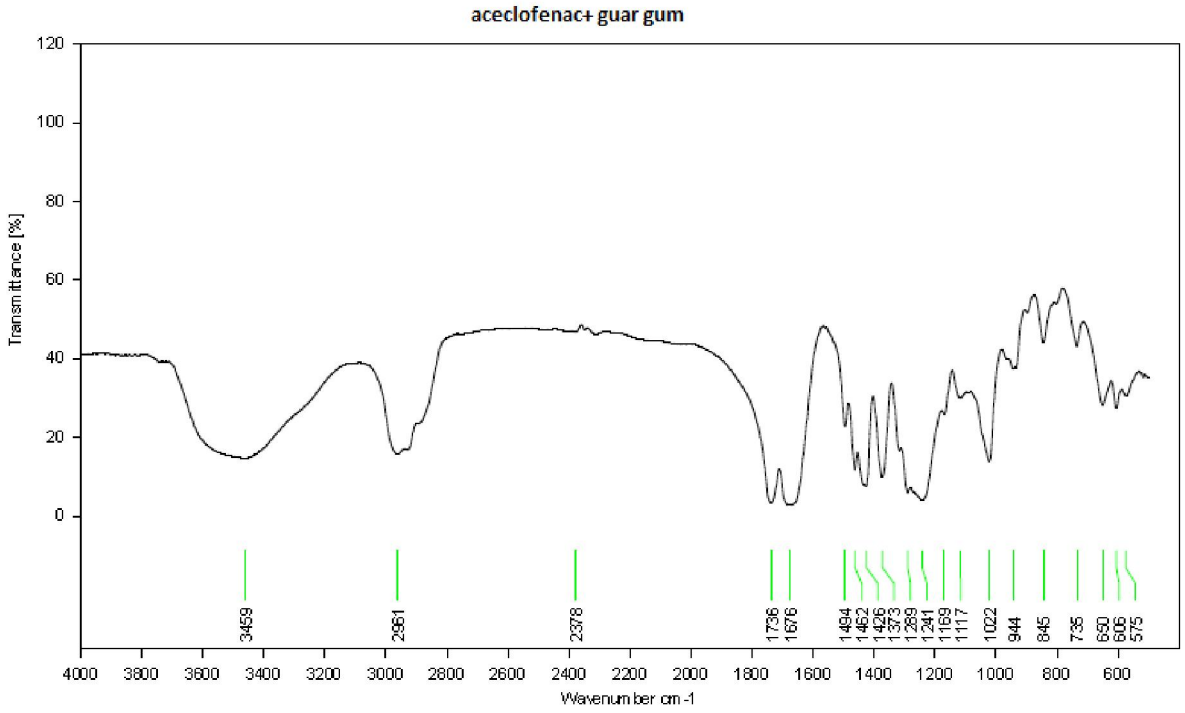


Fig 22 FTIR of Aceclofenac + guar gum

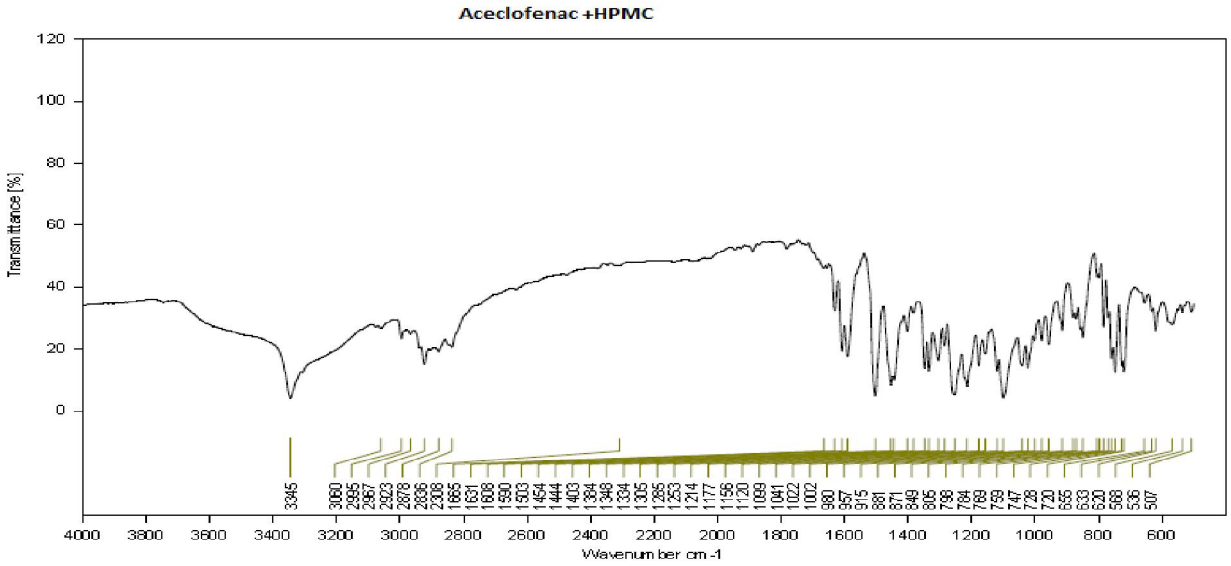


Fig 23 FTIR of Aceclofenac + HPMC

B. Evaluation of Floating Tablets

It is always necessary that the dosage forms prepared have to be evaluated for their characteristic properties. Hence quality control tests of tablets are performed to assess various properties of tablets.

Table 7 Preformulation –Flow properties

Formulation	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio (HR)
AF1	28.1±0.01	0.57±0.01	0.71±0.04	1.24±0.01
AF2	26.3±0.02	0.55±0.02	0.67±0.03	1.22±0.02
AF3	27.6±0.03	0.55±0.01	0.70±0.01	1.27±0.03
AF4	26.9±0.04	0.54±0.03	0.73±0.03	1.35±0.01
AF5	26.9±0.05	0.53±0.04	0.67±0.03	1.26±0.02

i. **Weight variation:** tablets exhibit variation due to improper filling of die cavity, uneven distribution of ingradients in the compression and variation in conmpressional pressure.

The total weight of each formulation is not maintained constant but the weight variation is in the range of +/-5% w/w indicating good control of compression process

Table 8 Weight Variation for (AF1-AF5)

S.NO	FORMULATIONS	WEIGHT VARIATION (mg)
1	AF1	460±0.12
2	AF2	462±0.34
3	AF3	460±0.33
4	AF4	460±0.33
5	AF5	457±0.42

ii. **Friability:** It is a measure of tablet strength. It is related to tablets ability to withstand both shock and abrasion without crumbing during the handling of manufacture, jacking, shipment and consumer use.

The friability was determined as the percentage loss in the weight of the tablets. A loss of less than 0.5 to 1% in weight is generally considered acceptable.

Table 9 Percentage Friability for (AF1-AF5)

S.NO	FORMULATIONS	FRIABILITY (%)
1	AF1	0.25±0.01
2	AF2	0.30±0.06
3	AF3	0.45±0.04
4	AF4	0.55±0.02
5	AF5	0.21±0.03

iii. **Hardness:** Hardness was measured using Pfizer hardness tester which measure the pressure required to break the diametrical placed tablets by the pressure with coiled spring.

Table 10 Hardness for (AF1-AF5)

S.NO	FORMULATION	HARDNESS
1	AF1	4.5±0.2
2	AF2	5.0±0.1
3	AF3	4.5±0.12
4	AF4	5.0±0.16
5	AF5	5.5±0.09

iv. Thickness: the thickness of the tablet is measured by using screw gauge. It gives the changes in weight variation of the tablet

Table -11 Thickness for (AF1-AF5)

S.NO	AF1	THICKNESS (mm)
1	AF2	3.0±0.01
2	AF3	2.9±0.05
3	AF4	3.1±0.02
4	AF5	3.2±0.02
5	AF1	3.0±0.02

v. **Floating lag time:** the floating lag time is determined in order to assess the time taken by the dosage to float on the top of the dissolution medium, after placing the dosage form in the medium

Table 12 Floating lag time (sec) & Floating time (hrs) for (AF1-AF5)

S.NO	FORMULATION	FLOATING LAG TIME (sec)	FLOATING TIME (hrs)
1	AF1	30	8
2	AF2	120	9
3	AF3	40	6
4	AF4	75	6
5	AF5	240	9

vi. **Drug content:**

Table 13 % Drug content for (AF1-AF5)

S.No	Formulation	Drug content (%)
1	AF1	98.5±0.1
2	AF2	97.2±0.2
3	AF3	98.1±0.6
4	AF4	97.5±0.5
5	AF5	98.3±0.1

C. **Dissolution studies:** freshly prepared dissolution medium i.e 900ml 0.1N HCl in each dissolution vessel of dissolution paddle apparatus maintained at temperature $37^{+/-}$

0.5^0C and rotated at 75 rpm. The tablets of aceclofenac were placed in dissolution medium. About 5ml of the dissolution medium was pipetted out for every 15, 30, 60, 120, 240, 480, 960 min and the volume was adjusted using by replacing with 5ml of 0.1N HCl**.** The above samples i.e 5ml (7 samples) were collected in a volumetric flask and make up the volume to 10ml with 0.1N HCl. Finally the absorbance of the solution was taken using UV spectrometer at 275 nm.

Table-14 Percentage Cumulative Drug Release

TIME(h)	**% CUMULATIVE DRUG RELEASE**				
Formulations	**AF1**	**AF2**	**AF3**	**AF4**	**AF5**
0	0	0	0	0	0
1	20.3	12.8	16.9	17.9	13.6
2	43.5	13.2	24.3	22.7	21.6
4	59.1	28.9	32.5	36.3	33.6
8	72.6	37.1	46.3	44.3	44.8
12	80.4	46.5	59.7	56.6	62.3
16	85.2	56.9	72.2	72.6	71.3
20	95.3	62.2	86.9	82.1	76.8
24	98.4	72.2	88.3	84.1	80.3

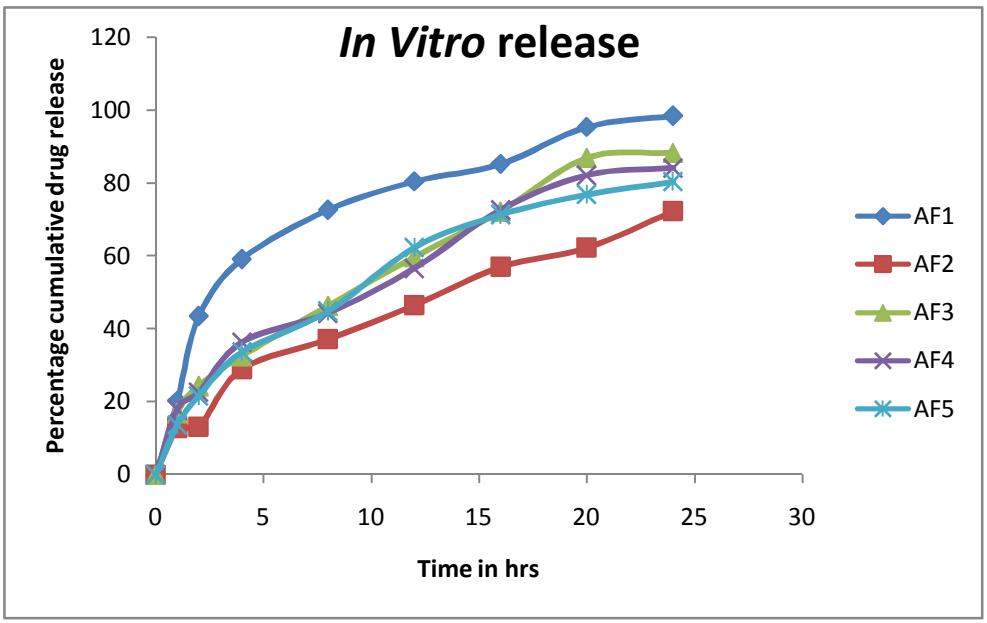


Fig 23 Cumulative % Drug Release curve

7. SUMMARY AND CONCLUSION

Floating drug delivery systems prolongs the gastric residence time which in turn produces increased drug bioavailability. Due to its less density than the aqueous medium, it floats in the gastric fluid. These drug delivery systems are suitable in the stomach or in upper small intestine due to its narrow absorption window.

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

In this present project, aceclofenac was used as a model drug for the floating tablets. Aceclofenac is used in the treatment of inflammation, and it is used as analgesic, anti-arthritic agent also.

Aceclofenac decrease pain and suppresses the disease severity and improves the therapeutic efficiency. It reduces pain in joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis.

Floating tablets of aceclofenac were developed to prolong gastric residence time and increase its bioavailability.

Floating tablets of aceclofenac were prepared using individual and combination of polymers. The polymers HPMC, Carbopol 940 and guar gum were used in different ratios. Totally five formulations (AF1-AF5) were designed and formulated. The flow properties bulk density, tap density, angle of repose for the granules was determined and the results were found to be within the limit for all the formulations. The aceclofenac floating tablets were prepared by direct compression method. The direct compression method is easy, simple and

time consuming. These formulations (AF1-AF5) were evaluated for various tests like weight variation, content uniformity, friability, hardness and dissolution studies.

The hardness and friability of the tablets were within the limits for all the formulations.

The weight variation of the tablets was found to be within the limits.

The content uniformities of the prepared tablets were found to be within the limits. The floating lag time for the prepared formulation was ideal for the floating drug delivery systems.

The percentage drug release of the formulations AF1, AF2, AF3, AF4 and AF5 was 98.4, 72.2, 88.3, 84.1 and 80.3 up to 24 hour

The formulation (AF1) prepared with HPMC showed good floating time and formulation (AF2) with carbopol 940 showed good floating time i.e 8 hours.

The formulation (AF1) with hydroxypropylmethyl cellulose was found to be best formulation with floating time of 8 hrs and drug release of about 98.4% at the end of 24^{th} hour.

This present research work focuses on the floating tablets of aceclofenac, and succeeded in the formulation. But still research to be continued to in vivo studies to prove the effectiveness of the prepared aceclofenac floating tablets.

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